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Treatment of Unresectable or Metastatic Pediatric Soft Tissue Sarcomas With Surgery, Irradiation, and Chemotherapy: A Pediatric Oncology Group Study

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Background. The objectives of this study were to compare vincristine/actinomycin D/cyclophosphamide/adriamycin (VACA) with VACA plus imidazole carboxamide (DTIC) (VACAD) therapy in regards to complete/partial response and event free survival rates in children and adolescents with metastatic non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) or previously chemotherapy-naive recurrent NRSTS or locally persistent gross residual tumor after surgery and radiation therapy.

Procedures. Between 1986 and March 1994, 75 patients entered this randomized study comparing VACA and VACAD, given at 3 week intervals. Sixty-one patients were considered eligible and received chemotherapy and radiation therapy to the primary tumor and areas of metastases. Thirty-six patients had regional unresected (Group III) disease, and 25 had metastatic disease (Group IV) at time of accession. Thirty-six patients received VACA (11 were not randomized), and 25 received VACAD.

Results. With a median follow-up of greater than 4 years, overall and event-free survival for all eligible patients are 30.6% and 18.4%, respectively (S.E: 9.5% and 6.8%). There was insufficient evidence that DTIC offered any advantage to event free survival, but there was evidence for better outcome for patients in Group III disease in comparison to patients with Group IV disease, and for patients with a Grade 1 and 2 histology in comparison to Grade 3 lesions.

Conclusions. Combination chemotherapy with VACA and VACAD were insufficient to prevent recurrent or progressive disease in children and adolescents with high stage NRSTS. The use of vincristine/ifosfamide/doxorubicin with cytokine support is under study. Med. Pediatr. Oncol. 30:201–209, 1998.

Key words: sarcomas; non-rhabdomyosarcoma; stage; tumor grade; childhood tumors

INTRODUCTION

Soft tissue sarcomas (STS) are the fifth most common form of cancer encountered in individuals less than age 15 years [1,2]. Among these STS, rhabdomyosarcoma is the most frequent type, accounting for three-fourths of all STS. Non-rhabdomyosarcoma soft tissue sarcomas encompass many histologies but are less frequently encountered, and less has been known about their natural history [3–20].

In the past, randomized therapeutic trials involving children with these rare tumors have not been performed in the United States. This communication reports such a trial, as initiated in 1986 by the Pediatric Oncology Group for patients with unresectable or metastatic non-rhabdomyosarcoma soft tissue sarcomas (NRSTS).

MATERIALS AND METHODS

The objectives of this study (POG 8654) were to study the tumor histology of patients with gross residual or metastatic NRSTS after surgery and radiation therapy at diagnosis, or previously ''untreated'' recurrent NRSTS (patients who had received no ''adjuvant'' chemotherapy

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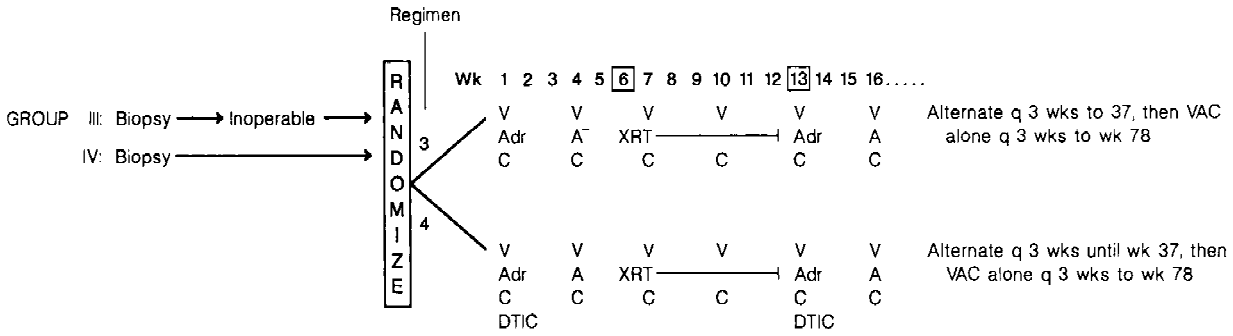

Fig. 1. Schema for POG 8654.

or radiation therapy on a companion study for IRS Groups I/II NRSTS, POG 8653) [21], and to compare vincristine/actinomycin D/cyclophosphamide/doxorubicin (VACA) with VACA plus imidazole carboxamide (dacarbazine; VACAD) in regard to complete response and relapse-free survival rates.

Further objectives of the study were to determine whether adjuvant chemotherapy with VACA increased the event free survival rates for patients who were in complete response after surgery ± radiation. Additionally, this protocol compared the complete response rates and relapse free survivals and event free survival rates for patients with Groups III and IV NRSTS. These objectives allowed the study of the histology of the soft tissue sarcomas and correlated the findings with clinical characteristics of their diseases and prognosis. Treatment consisted of surgery, chemotherapy, radiation therapy, as outlined below and depicted in Figure 1.

Chemotherapy

Chemotherapy consisted of vincristine 1.5 mg/m^2 (maximum dose = 2.0 mg) given IV push or by infusion over 15 minutes, one dose on day 1 of each 3-week cycle; top dose was 2 mg. Actinomycin D was given in a dosage of 1 mg/m^2 IV (no maximum dose) push, one dose on day 1 of each cycle; a top dose was not prescribed. Cyclophosphamide 750 mg/m^2 (no maximum dose) was given IV by infusion in 15 minutes, one dose on day 1 or each cycle, without a top dose; maintenance fluids were delivered in a volume of 250 ml/m^2/hr for 4 hours after the cyclophosphamide infusion. Doxorubicin 60 mg/m^2 was given by IV push or by infusion in 15 minutes, one dose on day 1 of each cycle; the maximum cumulative dosage was 360 mg/m^2. DTIC 500 mg/m^2 was given by IV infusion, one dose on day 1 of each cycle; no top dose was prescribed.

Dosage modifications were made for infants less than 12 months of age, for whom the initial dose of each agent was decreased by 50%; if that dosage was tolerated with an absolute neutrophil count (ANC) of greater than 500 μl and platelet count of at least 50,000 μl, dosage was increased to 75% and then to 100%. For older children, ANC of less than 500 μl or platelet count of less than 50,000 μl were reasons to delay chemotherapy for at least 1 week.

Patients were stratified by clinical groupings, as defined by Intergroup Rhabdomyosarcoma Study criteria [21]. For clinical Group III, gross residual tumor after initial surgery, the tumor was expected to be operable and completely resectable after radiation therapy. Radiation therapy was delivered to the tumor bed.

Subsequent chemotherapy administration was with full dosage if ANC was >500 μl and platelet count >50,000 μl. If at any time ANC was <250 μl, or platelets <10,000 μl, subsequent actinomycin D, cyclophosphamide, and doxorubicin were decreased by 25%. Omitted dosages were delivered at later periods, if possible.

Patients with clinical Group III disease and unresectable tumors, and those with clinical Group IV tumors were randomized to receive VACA or VACAD, in which actinomycin D and doxorubicin were alternated at 3 week intervals. During radiation therapy (weeks 6–12), only vincristine and cyclophosphamide were delivered, with omission of cyclophosphamide during that time if the bladder was in the radiation portal. After completion of radiation therapy, VACA was alternated with VAdrC or VACAD until week 40, after which no further doxorubicin was given. For those patients who received DTIC, this agent was given on those weeks when VAdrC was given. The total dosage of doxorubicin planned for all patients was 360 mg/m^2.

Radiation Therapy

Patients with clinical groups III and IV tumors were treated with megavoltage irradiation to the site of the primary tumor, the particular dosage being determined by the operability, site of tumor, and age of the patient. It was planned that patients with clinical group IV tumor also would receive radiation therapy to metastatic sites. Parallel opposed portals usually were used with both fields being treated each day. In general, the total dosages delivered, which included treatment guidelines relative to

the patient's age, were 35 Gy to the initial tumor volume (5 cm margins in all directions), with 45 Gy dosage to a reduced tumor volume (2 cm margin in all directions) and boost of total dosage of 55 Gy to tumor volume (inoperable and clinical Group IV, original volume completely encompassed) for children less than age 6 years, and for children 6 years of greater 45 Gy to the initial tumor volume (5 cm margins in all directions), 50 Gy to a reduced tumor volume (2 cm margins in all directions), and 65 Gy to total dosage of tumor volume. In view of the heterogeneity of tumor sites and adjacent normal tissue, variations were permitted if discussed in advance with one of the coordinators (P.R.M.T. or R.B.M.) and a minimum of 30 Gy given. Radiation therapy was delivered to the primary tumor and sites of metastases starting at week 6. The total dosages were based upon a consideration of a daily dose rate of 1.8 Gy per day, delivered 5 days per week. Special consideration was given to sparing of normal tissues, including the kidneys, liver, lung, and heart. Treatment to metastatic disease sites including lungs, whole abdomen (peritoneal implants), bones, and brain, required specific prescription. Children under 2 years of age, and especially those under 1 year of age, had treatment modifications relative to port size and/or dosage given.

Evaluation of Effects of Treatment

The effects of chemotherapy were evaluated for response and/or recurrence at week 6, and the effects of radiation therapy were evaluated at week 13 for response and/or recurrence. The results that are recorded are for the combined effects of chemotherapy and radiation therapy.

In addition to clinical examination and imaging studies for anatomical region(s) of involvement, the primary tumor (T), regional lymph nodes (N), and metastatic sites (M) were assessed (TMN). Histopathologic grading was assessed according to POG criteria, dividing the tumor into low grade (G1), moderate (G2), and high grade (G3) lesions [22–25].

Toxicity was quantitated by the Common Toxicity Criteria of the National Cancer Institutes.

Surgery

Surgery guidelines included diagnostic biopsy for NRSTS not in body cavities, and definitive surgery such as an initial attempt at therapeutic resection for local control, with considerations for anatomic feasibility for resection and/or disability. Second-look surgery for Group III patients was delayed for 6–12 weeks after completion of radiation therapy. The final decision regarding which Group III lesions were potentially resectable after irradiation was a responsibility of the surgeon.

Anatomical limitations were considered for the mediastinum and retroperitoneum, and for certain head and neck, trunk, and extremity lesions which would require major ablative surgery for total removal. Group III lesions were defined as those with incomplete resection and gross residual disease after biopsy only, or after gross or major resection. Group IV lesions were those with distant metastatic disease present at onset (i.e., lung, liver, bones, bone marrow, brain, distant muscle, and distant nodes).

Pathology

Tumors included as Grade I lesions included myxoid and well-differentiated liposarcoma, dermatofibrosarcoma protuberans, well-differentiated leiomyosarcoma, well-differentiated malignant hemangiopericytoma, well-differentiated malignant tumor of peripheral nerve sheath, and myxoid chondrosarcoma (uniformly myxoid, hypocellular with virtually no mitoses) [24,27].

Grade II Lesions were those STS not specifically included in Grades I and III. Grade III lesions included pleomorphic liposarcoma, mesenchymal chondrosarcoma, soft tissue osteosarcoma, malignant Triton tumor, alveolar soft part sarcoma, and synovial sarcoma (provided that these tumors had >15% surface necrosis, >5 mitosis per 10 high power fields, dense cellularity with pleomorphism) [24,25].

Statistical Design

The statistical design assured a 25% response rate for VACA, and was planned to detect a 40% response rate for VACAD with 80% power, using a Type I error of 5%. It was determined that 94 patients would be required; and, based on accrual rates at the time, it was estimated that the study would require 4.2 years to accrue 94 patients.

RESULTS

This study opened in June 1986 and accrued a total of 75 patients before closing March 1994. The study was closed in March 1994 prior to obtaining the target accrual of 94, because of slow accrual accompanied by investigator bias related to randomization. Among the 75 patients, 14 were declared ineligible primarily because the central pathologic review determined that they had tumor histologies excluded from the study, in disagreement with the original institutional pathologic findings (rhabdomyosarcoma 6, malignant lymphoma 2, fibromatosis 1, osteosarcoma 1, thymoma 1, other 2, and no consent form 1). Patient demographics are as noted in Table II, and diagnoses of the evaluable patients are as listed in Table I. Among the 61 eligible patients, 33 were males. Median age of these patients was 11.8 years (range 3 days to 21.7 years). The racial distribution was as follows: Caucasian 41, Black 10, Hispanic 3, and Oriental 1. Two patients had previously been enrolled on POG

TABLE I. Distribution of Tumors, by Histology of Eligible Patients

Malignant peripheral nerve sheath tumor	13
Synovial sarcoma	8
Sarcoma, not otherwise specified	6
Alveolar soft part sarcoma	5
Malignant fibrous histiocytoma	5
Fibrosarcoma	4
Hemangiopericytoma	4
Leiomyosarcoma	3
Embryonal sarcoma of liver	2
Epithelioid sarcoma	2
Clear cell sarcoma of tendons	2
Malignant mesenchymoma	2
Neuroepithelioma	2
Hemangioendothelioma	1
Hemangiosarcoma	1
Mesothelioma	1
	61

8,653 and were treated after regional recurrence (initially Group I disease) or distant metastases (initially Group II disease).

Patients or parents initially were offered the opportunity for randomization to VACA or VACA plus DTIC (VACAD) chemotherapy. Between August 22, 1991 and September 1992, patients were assigned the VACA arm because of a shortage of DTIC. Randomization was restarted in September 1992. Of the 61 eligible patients, 11 were not randomized (and assigned to the VACA arm), 25 were randomized to VACA, and 25 were randomized to VACAD.

Response

Response of the eligible patients by clinical group is given in Table II and by chemotherapy regimen is given in Table III. A comparison among the randomized patients (VACA vs. VACAD) of the response rates (complete responses and partial responses) to the two chemotherapy regimens using Fisher's exact test was not statistically significant ($P = .4$). Exact 95% confidence intevals for the response rates of the randomized patients are (35%, 76%) for VACA and (24%, 65%) for VACAD.

Complete responses were recorded for 2/8 with synovial sarcoma and 4/13 with malignant tumor of peripheral nerve sheath.

Survival and Event-Free Survival

For all eligible patients, overall survival and event-free survival at 4 years are 30.6% (SE = 8.5%) and 18.4% (SE = 6.8%), respectively (Fig. 2). Among the randomized patients, the 2-year event free survival is 36% (SE = 10.2%) for the VACA arm and 26.4% (SE = 9.2%) for the VACAD arm (Fig. 3), as stratified by group. A one-sided log rank test comparing the event free survival distributions provided insufficient evidence that the addition of DTIC offered any advantage in terms of event-free survival to this cohort of patients ($P = .7$).

TABLE II. Response by Clinical Group (Randomized Patients Only), Treatment by POG8654 Protocol

Clinical group	Not evaluable	Complete response	Partial response	Mixed response	No response
III	1	14[a]	5	0	16
IV	0	3	6	3	13

[a]One patient was chemotherapy- and radiation-naive after having local recurrence while being followed by POG 8653 protocol.

Event free survival by group, comparing clinical groups III and IV is shown for all eligible patients in Figure 4. As expected, patients with group IV disease had significantly reduced event free survival ($P = .01$). There was insufficient evidence to demonstrate a difference in event free survival between grades 1, 2, or 3 ($P = .4$). However, only 13/52 patients had tumor grade 1 or 2. Combining grades 1 and 2 and comparing to grade 3 also failed to show a difference in event-free survival ($P = .2$), although it appeared that the grade 3 failures were occurring earlier (Fig. 5).

Toxicity

Grade 3 or 4 toxicity for 61 evaluable patients receiving VACA or VACAD was comparable. There were no toxic deaths associated with either surgery, radiation therapy, or chemotherapy. Regarding the severity of the toxicity among 27 patients evaluable for toxicity following VACA, only six had Grade 4 ANC (<500 μl) and only two had Grade 4 ANC counts with the five-drug combination. The toxicity was generally mild except for bacterial and/or viral infection. Alopecia was rarely recorded. A few doses were delayed because of mucositis or myelosuppression.

Outcome

Table IV summarizes the current status of all patients by clinical groupings. Information regarding sites of failure is not specifically given since all patients had significant loco-regional disease (Group III) or loco-regional plus metastatis disease at diagnosis (Group IV). Overall, 16/36 patients with Group III disease and 13/25 with Group IV disease had no response at all to chemo-radiotherapy.

DISCUSSION

The NRSTS occur with a frequency equal to about one-fourth of that of rhabdomyosarcoma. These tumors have varying names, but yet little is known about the prognosis for specific groups of patients with varying stages of disease. However, it is known that factors influencing local control or survival of patients with

TABLE III. Responses by Chemotherapy Regiment for NRSTS Patients*

	Not evaluable	Complete	Partial	Mixed	No response	CR + PR
VACA						
Randomized	1	4	6	2	8	14/25 (56%)
Non-randomized	0	2	1	0	8	3/11 (27%)
VACAD	0	7	4	1	13	11/25 (44%)
	1	17	11	3	29	20/61

*VACA = Vincristine, actinomycin D, cyclophosphamide, doxorubicin; VACAD = Vincristine, actinomycin D, cyclophosphamide, doxorubicin, dacarbazine.

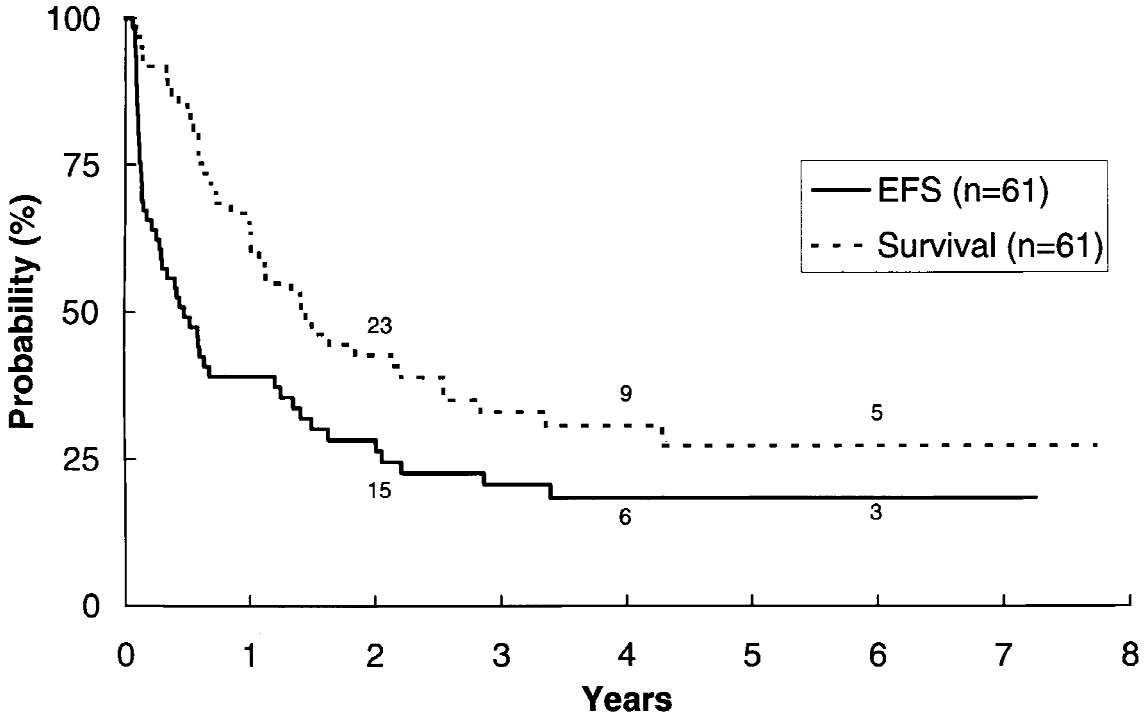

Fig. 2. Survival and event free survival of patients with clinical Groups III and IV NRSTS.

NRSTS include adequacy of treatment by surgery, with or without chemotherapy or radiation therapy. In a companion to this study, POG 8653 determined that for Group 1 and Group 2 lesions, chemotherapy, and radiation therapy were not required following complete removal of tumor [22,23]. There was some question as to which Grade 3 lesions, if any, should require irradiation or chemotherapy, in spite of resectability. This protocol, and the work of others, indicated the influences of tumor size and grade, and suggested that patients with histologic Grade 3 and invasive lesions T_2 and $T_{2B} > 5$ cm should be enrolled on effective chemotherapy protocols [24–26,28,29].

This protocol (POG 8654) is the first multi-institutional trial effort for treatment of NRSTS in the United States. Accrual was slow because of lack of previous information on the responsiveness of tumors of this variety to chemotherapy and/or irradiation. In Europe, the NRSTS are treated by the malignant mesenchymal tumor (MMT) protocols of SIOP or similar protocols with the various national pediatric oncology programs such as in Germany, France, and Italy [29–33].

Most of the patients in this protocol had either malignant tumor of peripheral nerve sheath, synovial sarcoma, sarcoma not otherwise specified (N.O.S.), alveolar soft part sarcoma, or malignant fibrous histiocytoma. This distribution varies from that of most NRSTS of adults, where there is a preponderance of fibrosarcoma, malignant fibrous histiocytoma, leiomyosarcoma, and liposarcoma. All of the tumor types encountered in this series of tumors are probably more commonly encountered in adults than in the pediatric patients [3]. These pediatric NRSTS apparently have a similar natural history to similarly named tumors of adults.

There was a significantly increased event free survival of individuals with Group III lesions in comparison to Group IV lesions (Fig. 4) as well as a significantly increased benefit in survival comparing tumor Grades 1

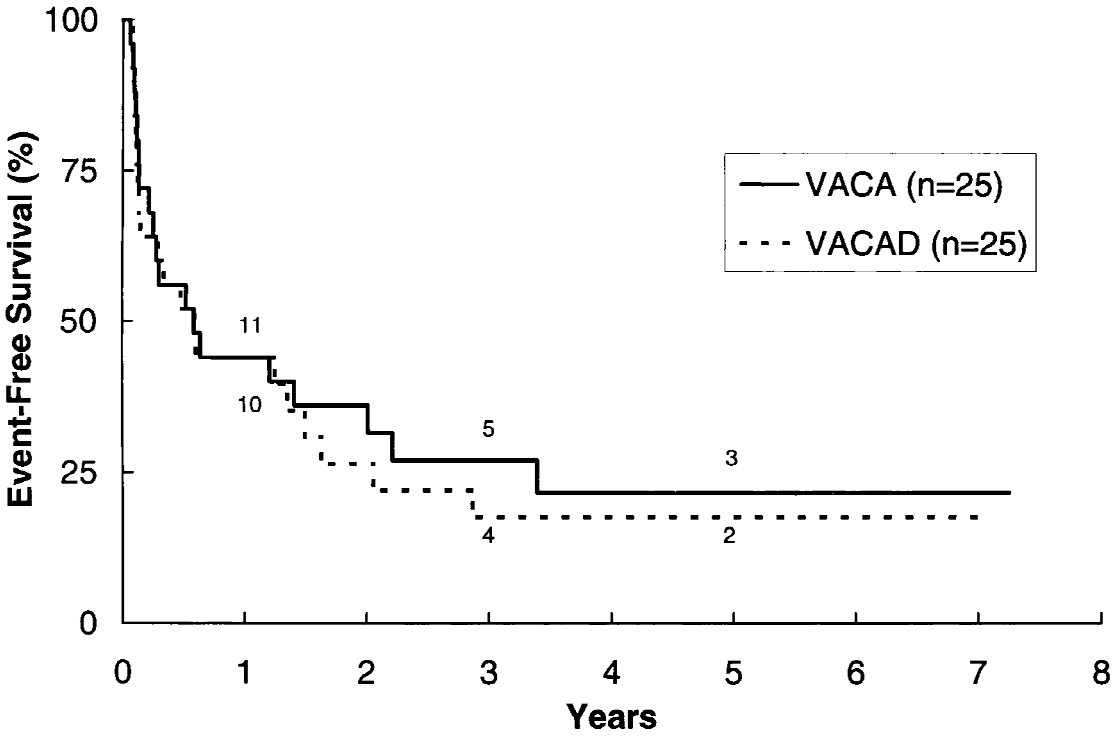

Fig. 3. Event free survival by chemotherapy treatment received (randomized patients only).

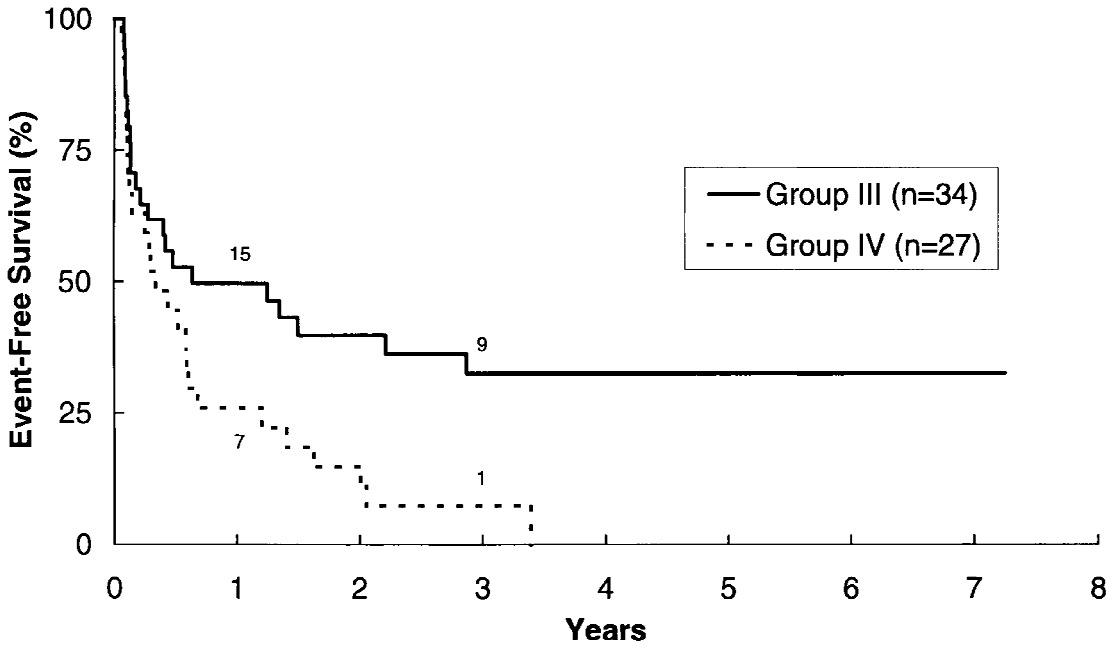

Fig. 4. Event free survival of NRSTS patients by clinical group.

and 2, with 3. This was also true for event free survival when compared by tumor grade ($P = 0.143$; Fig. 5). Overall, the 3 year survival and event free survival were 30.6% (SE = 8.5%) and 18.4% (SE = 6.8%), respectively. For randomized patients, 2-year event free survival was 36% (SE = 10.2%) for the VACA arm and 26.4% (SE = 9.2%) for the VACAD arm (Fig. 3). A one-sided stratified (by group) log-rank test comparing the event free survival distributions indicated no advantage for either treatment ($P = 0.706$).

For all patients with NRSTS, surgery continues to be recommended as the initial treatment of choice

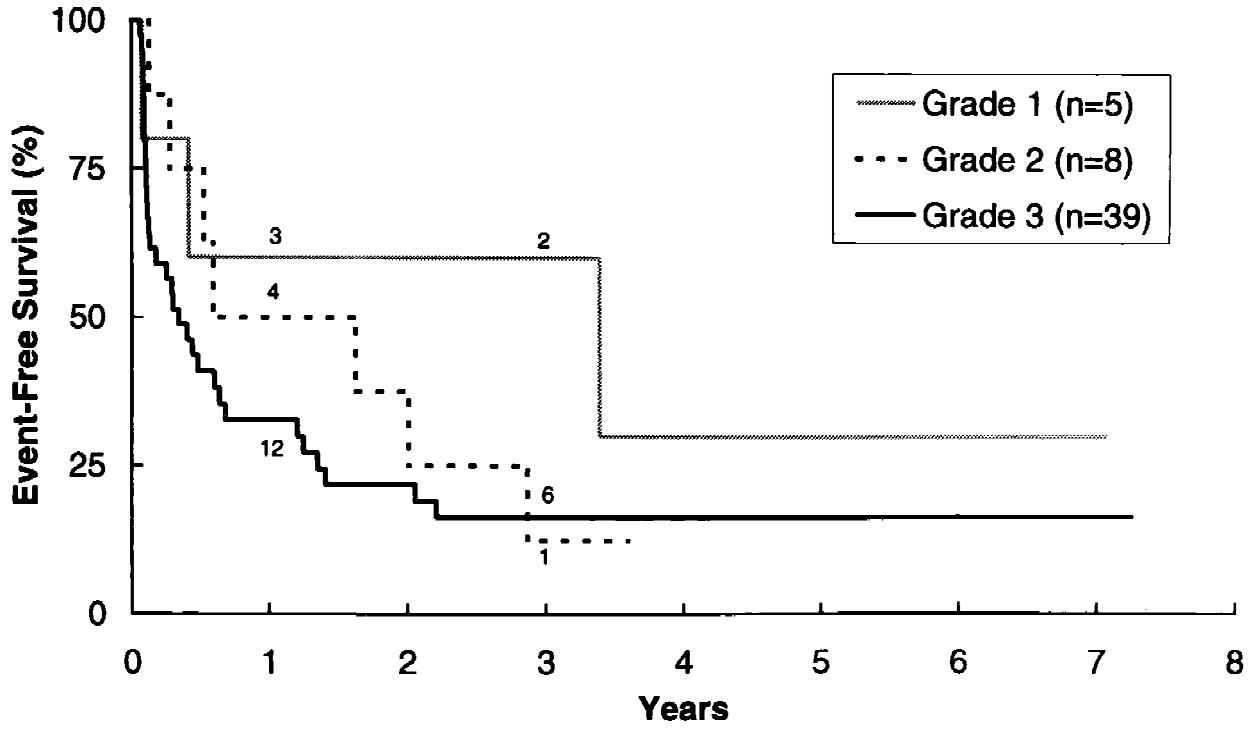

Fig. 5. Event free survival of NRSTS patients by tumor grade.

TABLE IV. Outcome Following Treatment by POG 8654

Group III	Group IV
7 Continuing complete response	1 Continuing complete response
1 Complete response, lost to follow-up	1 Complete response, death from other causes
5 Complete responses, relapses, death	1 Complete response—recurrent disease, death
1 Complete response,—refused further treatment, death	5 Partial responses—progressive disease, death
1 Early death (from tumor)	1 Partial response—refused further treatment, death
5 Partial responses, —progressive disease, death	3 Mixed responses, —progressive disease, death
16 No response, death	13 No response, death
36	25

[6,8,39,40]. Initial surgery may include biopsy, laparotomy, thoracotomy, or endoscopic biopsy, including minimal invasive surgical procedures. For those lesions considered resectable, surgical procedures include wide local resection, en bloc or compartmental resection, or amputation. When a wide margin (about 2 cm) is not feasible, local control may be obtained with the use of radiation therapy. Pre-operative chemotherapy, preoperative radiotherapy, or both may facilitate later definitive surgical procedures.

The role for chemotherapy for clinical Groups III and IV NRSTS remains unclear because of the many histologic subtypes of tumors included within the patient population [13,23,27]. Chemotherapy delivered to the participants of this protocol was ''mild'' in comparison to chemotherapy protocols as used today for soft tissue sarcomas of adults [41–45] and for such tumors as rhabdomyosarcoma or the Ewing's family of tumors [46], with or without cytokine or stem cell factor support. More predictive, however, as determined from this and other single institution experience, is the fact that tumor size, invasiveness, and tumor grade and unresectability all contribute to the overall outcome for both adult and pediatric NRSTS [5,27].

There was no evidence that addition of DTIC to VACA offered any advantage in terms of event free survival to this group of patients [47–49]. The dose intensity of DTIC, however, was minimal throughout its delivery. However, because of the difficulty in accruing patients, this comparison had lower power than planned. Neither chemotherapy regimen was satisfactory in treating patients with Group III or IV NRSTS. Event free and overall survival were poor, with survival of Group IV patients with NRSTS similar to Group IV patients with rhabdomyosarcoma. Radiation therapy had an important role in the treatment of the patients on this protocol, as with other NRSTS of children and adults [47–49]. However, the extent of primary and metastatic disease influenced the surgery and radiation that were feasible for these patients.

This protocol was conceived and initiated prior to the FDA approval of ifosfamide, which is regarded by many medical oncologists to be among the necessary agents for

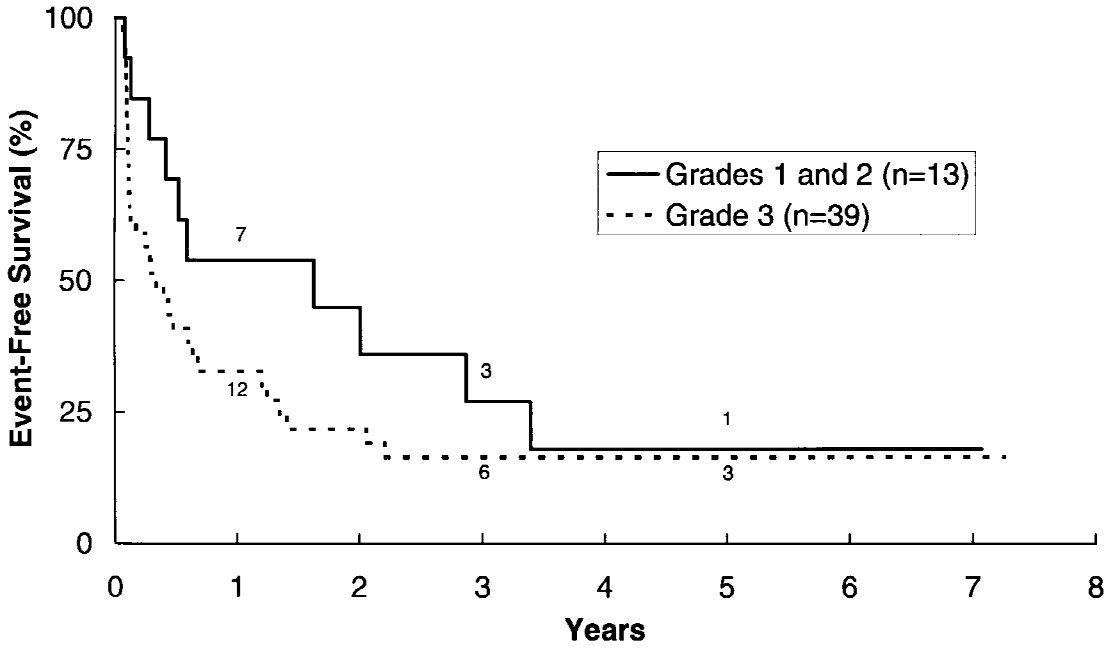

Fig. 6. Event free survival by tumor grade, comparing Grades 1 and 2 with Grade 3.

effecting cure of NRSTS in adults [42,43,45,50]. We recognize that more effective therapy is required for both Groups III and IV NRSTS and that such a protocol is in progress. As a successor to this protocol, the Pediatric Oncology Group has a nonrandomized study for patients with Groups III and IV NRSTS which includes surgery, radiation therapy, and chemotherapy with vincristine, doxorubicin, and ifosfamide. More intensive chemotherapy will be given over a shorter period of time with cytokine support and with similar surgical and radiation therapy guidelines. It is hoped that the effectiveness of this combination will be more dramatic than that seen with the two four- or five-drug combinations utilized in this study.

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